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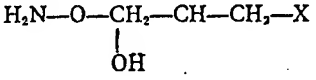
(54) ALKYLATED HYDROXYLAMINES

(71) We, HOECHST AKTIENGESELLSCHAFT, a Body corporate organised under the laws of the Federal Republic of Germany of 6230 Frankfurt/Main 80, Germany, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to *O*-alkylhydroxylamines having interesting pharmacological properties.

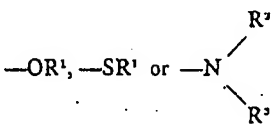
Many hydroxylamine derivatives, some having valuable biological properties, are known. Thus, for example, the preparation has been reported of some *O*-(2hydroxyalkyl)-hydroxylamines, without further functional groups in the alkyl radical, by the N-hydroxyurethane method of E Testa *et al.* [Helv. Chim. Acta *45*, 358, 1381 (1962)] and the N-hydroxyphthalimide method of W. Kliegel [Pharmazie *25*, 400, 525 (1970)].

According to one aspect of the present invention there are provided compounds of general formula



(I)

[wherein X represents a group of the formula



(in which R^1 represents

a) a hydrogen atom,
b) an amino group, when X represents an —OR^1 moiety,
c) an alkyl group having from 1 to 6 carbon atoms or
d) a mono- or binuclear aryl group optionally substituted by one or more halogen atoms or alkyl, alkoxy, halogenoalkyl groups each having up to 4 carbon atoms, cycloalkyl groups having 3 to 6 carbon atoms, nitro or cyano groups; and

R^2 and R^3, which may be the same or different, each represents

a) a hydrogen atom,

b) an alkyl group having from 1 to 6 carbon atoms or cycloalkyl group having from 3 to 7 carbon atoms and optionally substituted by one or more hydroxy groups or alkoxycarbonyl groups having 1 to 4 carbon atoms,

c) an aralkyl or diaralkyl group having 1 to 4 carbon atoms in the alkyl moiety and being optionally substituted in the alkyl moiety by hydroxy groups, and optionally substituted in the aryl moieties by one or more alkoxy groups having 1 to 4 carbon atoms or halogen atoms,

d) a mono- or binuclear aryl group optionally substituted by one or more alkyl, alkoxy or halogenoalkyl groups each having up to 4 carbon atoms or halogen atoms,

e) a hydroxy group when the other of R^2 and R^3 is hydrogen, or

f) R^2 and R^3, together with the nitrogen atom to which they are attached, represent a 5- to 7-membered saturated ring optionally substituted by an alkyl or hydroxyalkyl group each having from 1 to 4 carbon atoms, an aralkyl or diaralkyl group each having up to 4 carbon atoms in the alkyl moiety and the aryl moieties thereof are optionally substituted by one or more halogen atoms, a mono- or binuclear aryl group optionally substituted by at least one alkyl, alkoxy or halogenoalkyl group each having up to 4 carbon atoms, or by one or more halogen atoms or hydroxy groups; or by a 3-amino-2-hydroxylpropyl group, and the ring being optionally interrupted by an oxygen, sulphur or further nitrogen atom or sulphonyl group, or

g) R^2 and R^3 together with the nitrogen atom to which they are attached, represent a 5-membered heteroaromatic ring containing up to 4 nitrogen atoms and being optionally fused to one or more benzene or optionally substituted uracil rings)] and physiologically acceptable acid addition salts thereof.

In the compounds according to the invention, alkyl radicals in R^1, R^2 and R^3 may be straight-chained or branched. In the compounds of general formula I, R^2 and R^3 together with the nitrogen atom to which they are attached, preferably form a 5- to 7-membered ring having a further heteroatom which is nitrogen substituted by an alkyl or hydroxyalkyl group each having up to 4 carbon atoms; an aralkyl or diarylalkyl group each having up to 4 carbon atoms in the alkyl moiety and the aryl radicals thereof are optionally substituted by one or more halogen atoms; a mono- or binuclear aryl group optionally substituted by at least one alkyl, alkoxy, or halogenoalkyl group each having up to 4 carbon atoms, or by one or more halogen atoms or hydroxyl groups; or by a 3-amino-2-hydroxypropyl group.

Aryl groups in any of R^1, R^2 and R^3 of the compounds according to the invention, including any aryl substituents at a second N-atom of a saturated ring formed by R^2 and R^3, may be substituted one or more times, for example, up to three times. When R^2 and R^3 take the values given under b) and c) above, any hydroxyl group is preferably separated from the nitrogen atom in the group X, by 2 carbon atoms. An example of a binuclear aryl radical is the naphthalene system.

When R^1, R^2 and/or R^3 contain halogenoalkyl groups, these preferably contain 1 or 2 carbon atoms.

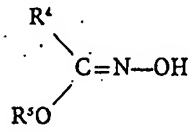
The compounds according to the invention exhibit interesting pharmacological properties. Depending on the nature of the substituent X they show blood-pressure-reducing. bronchospasmolytic, anti-convulsive, analgesic, antiphlogistic, chloreretic, uric acid-reducing, anthelmintic and antifungal activity. They may also be useful as starting substances for the synthesis of other pharmacologically active compounds, such as, for example, for the preparation of substituted *O*-(2-hydroxypropyl)-aldoximes from 2-formyl-5-nitroimidazoles or 2-formyl-5-nitrofuran, as described in our copending patent Application No. 46474/77 (Serial No. 1540030).

Preferred compounds according to the invention by reason of their favourable pharmacological properties are:

O-(3-phenoxy-2-hydroxypropyl)-hydroxylamine;
O-[3-(*p*-chlorophenoxy)-2-hydroxypropyl]-hydroxylamine;
O-[3-(2,4-dichlorophenoxy)-2-hydroxypropyl]-hydroxylamine;
O-[3-(3-methylphenoxy)-2-hydroxypropyl]-hydroxylamine;
O-[3-(4-methoxyphenoxy)-2-hydroxypropyl]-hydroxylamine;
O-[3-(4-cyanophenoxy)-2-hydroxypropyl]-hydroxylamine;
O-[3-(3-trifluoromethylanilino)-2-hydroxypropyl]-hydroxylamine;
O-[3-(4-diphenylmethyl-piperazin-1-yl)-2-hydroxypropyl]-hydroxylamine and physiologically acceptable acid addition salts thereof.

According to further aspects of the present invention there are provided the following processes for the preparation of compounds of general formula I:—

a) reacting a hydroximic acid ester of formula

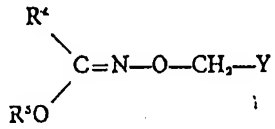


(II)

with a compound of formula

(III)

or b) reacting an *O*-alkylated hydroxylamine derivative of formula

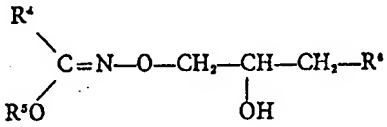


(IV)

with a compound of formula

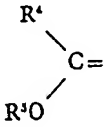
(V)

in each case to form a common intermediate compound of formula



(VI)

and subsequently removing the protecting group of formula



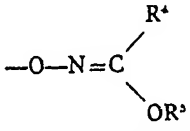
to form a compound of formula I.

In the above formulae:—

R^4 represents a straight-chained or branched alkyl group having from 1 to 6 carbon atoms or a mono- or binuclear aryl group optionally substituted by one or more alkyl or alkoxy groups having up to 2 carbon atoms or halogen atoms;

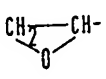
R^5 represents a straight-chained or branched alkyl group having from 1 to 6 carbon atoms;

R^6 is as hereinbefore defined for X or represents a group of the formula

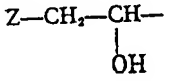


(in which R^4 and R^5 are as hereinbefore defined);

Y represents a group of the formula



or

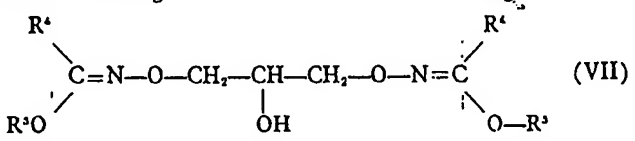


(in which Z represents a halogen, preferably chlorine or bromine atom, or a reactive sulphonic acid ester group).

The protecting group is preferably removed hydrolytically as a compound of formula R^4COOR^5.

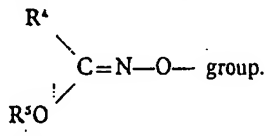
If in the above process the compounds of general formula I are produced as their free bases they may, if desired, be converted with suitable acids into the corresponding physiologically compatible acid addition salts in known manner.

In the synthesis of compounds of general formula I according to the above processes in which X represents the group $-O-NH_2$, an intermediate compound protected on both sides having the formula



(VII)

(wherein R^4 and R^5 are as hereinbefore defined) may be obtained when using a compound of formula III or V in which R^6 represents an



group.

Especially useful compounds of formula II are alkyl esters having from 1 to 4, and preferably 1 or 2 carbon atoms in the alkoxy group, such as, for example, methyl benzohydroximate and advantageously ethyl acetohydroximate. Such compounds can be readily prepared according to processes known *per se* from the corresponding imido esters and hydroxylamine [see for example J. Houben and E. Schmidt, Ber. dt. Chem. Ges. *46* 3619 (1913).

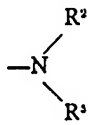
Starting compounds of general formula III are preferably 2,3-epoxypropyl derivatives which are generally known *per se* or can easily be prepared by processes known to those skilled in the art, for example, from epihalogenhydrins, especially epichlorohydrin, and nucleophilic compounds of general formula V in the presence of a base. The 2-propanols of formula III

$$Z-CH_2-CH(OH)-CH_2-X$$

(wherein X and Z are as hereinbefore defined) are similarly suitable as starting compounds and can be prepared, in principle, in the same way, but with the exclusion of basic condensation agents, from epoxides such as epichlorohydrin, epibromohydrin and 2,3-epoxypropylbenzenesulphonate, toluenesulphonate, 4-bromo-benzenesulphonate, or methanesulphonate.

The preferred process for the preparation of compounds I according to the invention comprises reacting the novel *O*-(2,3-epoxypropyl)-hydroximic acid esters of formula IV described in our copending Patent Application No. 46477/77 (Serial No. 1540030) with alcohols, thiols, phenols, thiophenols, amines or 5-membered aromatic nitrogen heterocycles of formula V according to alternative process b). In this case the alkyl *O*-(2,3-epoxypropyl)-benzohydroximates or alkyl *O*-(2,3-epoxypropyl)-acetohydroximates with 1 to 4, preferably 1 or 2 carbon atoms in the alkoxy group, e.g. methyl *O*-(2,3-epoxypropyl)benzohydroximate and especially ethyl *O*-(2,3-epoxypropyl)-acetohydroximate, have proved particularly useful.

The amines of formula V which may with advantage be used are those saturated cyclic compounds which are unsubstituted or which carry up to 4 alkyl radicals, preferably pyrrolidine, 2,5-dimethylpyrrolidine, piperidine, 2,6-dimethylpiperidine, 2,2,6,6-tetramethylpiperidine, hexamethyleneimine or compounds which contain an oxygen, sulphur or further nitrogen atom or sulphonyl group in the heterocycle and which are preferably separated by at least 2 carbon atoms from the nitrogen atom of the



group, such as, for example, morpholine, thiamorpholine, tetrahydro-1,4-thiazin-1,1-dioxide, piperazine and homopiperazine, where the second nitrogen atom of the heterocycle, e.g. the 4-position of a piperazine ring can carry, instead of hydrogen, optionally substituents such as, for example, the substituents indicated in Examples 47 to 62. Convenient 5-membered, aromatic, optionally fused, nitrogen-heterocycles are pyrrole, indole, pyrazole, indazole, imidazole, benzimidazole, triazole, benzotriazole, tetrazole, carbazole and xanthines such as theophilline.

The alkylation reactions according to processes a) and b) are conveniently effected in a solvent or dispersion agent which is inert towards the reactants under the reaction conditions, advantageously at temperatures between 0 and 200°C, preferably between 50°C and the boiling point of the reaction mixture, either in the presence of a base such as, for example alkali metal or alkaline-earth metal hydroxides, carbonates, hydrides and alcoholates or organic bases such as triethylamine, pyridine, picoline and quinoline or by use of alkali metal or alkaline-earth metal salts of the hydroximic acid esters of formula II or the alcohols, thiols, phenols, thiophenols and nitrogen heteroaromatic compounds of formula V. The reaction times may generally be from 1 hour to a few days.

Examples of solvents inert under the reaction conditions are, for example, anhydrous alcohols such as, for example, methanol, ethanol, propanol, isopropanol, butanol or isobutanol; ethers such as diethyl ether, diisopropyl ether, tetrahydrofuran, dioxane or diethyleneglycol dimethyl ether; hydrocarbons such as hexane, cyclohexane, petroleum ether, benzene, toluene or xylene; halogenated hydrocarbons such as dichloromethane, chloroform, carbon tetrachloride or chlorobenzene; aprotic solvents such as dimethylformamide, dimethylacetamide, N-methylpyrrolidone, tetramethylurea, hexamethylphosphoric acid trisamide, dimethylsulphoxide or acetonitrile; and, if desired mixtures of any of the above solvents.

Reaction of the hydroxylamine derivatives of formula II with epoxides of formula III according to process a) and the addition of thiols, phenols, thiophenols or nitrogen aromatic heterocyclic compounds of formula V to the oxiranes of formula IV according to process b), are preferably effected in dimethylformamide with the addition of triethylamine as catalyst at temperatures between 50 and 100°C. The starting compounds are advantageously used in equimolar quantities or with a slight excess of the alkylating agent.

On the other hand, alkylation according to process a) of a compound of formula II with the 2-propanols of formula III advantageously takes place using alkali metal or alkaline-earth metal hydroximates in alcoholic solution at reflux temperature.

Aminolysis of the oxiranes of formula IV with amines of formula V according to process b) is preferably effected by refluxing for 1 to 5 hours in alcohols having a higher boiling point than methanol, such as, for example, n-propanol (b.p. 97°C) or isopropanol (b.p. 82°C) in the absence of a further base, in which case primary amines are preferably present in an excess of up to 4 times the stoichiometric quantity.

In general, purification of the pure intermediate compounds of formula VI and VII obtained by the processes a) or b) is not necessary for subsequent hydrolytic removal of the protecting group. If desired, however, purification may be effected by fractional distillation under reduced pressure or, in some cases by crystallisation. Some intermediate compounds of formula VI thus isolated and analytically characterised are given in Table 3. Hydrolytic splitting of the protecting group from the intermediate is preferably carried out under acid conditions in aqueous, aqueous alcoholic or aqueous ether solution at temperatures from 0 to 120°C, advantageously from 60 to 110°C, the reaction time is usually between a few minutes and a few hours. Especially suitable for this reaction are dilute mineral acids such as hydrochloric acid and sulphuric acid. The *O*-alkylated hydroximic acid esters of formula VI are advantageous in that their protecting group can be separated as carboxylic acid esters of formula I R^4—$COOR^5$ quickly, gently and quantitatively under particularly mild reaction conditions.

As indicated above the products of the process according to the invention may be isolated either in the form of stable free bases or preferably as non-toxic acid addition salts. Suitable acids for the preparation of acid addition salts are, for example, halogen hydracids (such as hydrobromic acid and especially hydrochloric acid), sulphuric, phosphoric, acetic, lactic, maleic, fumaric, oxalic, tartaric, citric, gluconic, *p*-toluenesulphonic, methanesulphonic, benzenesulphonic and cyclohexylamido sulphonic acid.

It will be appreciated that the compounds of formula I according to the invention

have a chiral carbon atom and can thus exist as racemates or as optically active D or L isomers. All such forms are intended to be within the scope of the present invention.

In order to produce the individual optical isomers of the compounds of general formula I, processes a) and b) may be effected using enantiomeric starting compounds of formula III or IV or racemates obtained by these processes may be resolved into the optical isomers by means of processes known *per se*, e.g. by fractional crystallisation of the acid addition salts obtained from optically active acids.

As indicated above the compounds of general formula I according to the invention exhibit interesting pharmacological properties. Thus, according to a further aspect of the present invention there are provided pharmaceutical compositions comprising as active ingredient at least one compound of general formula I or a physiologically acceptable acid addition salt thereof in combination with a pharmaceutical carrier or excipient.

The compositions according to the invention may be conveniently administered orally or parenterally. Suitable solid or liquid forms of administration are, for example, granules, powders, tablets, capsules, syrups, emulsions, suspensions, drops or injectable solutions and forms adapted to provide a sustained release of active ingredient(s). Convenient carriers for use in the compositions of the invention are e.g. magnesium carbonate, various sugars, starch, cellulose derivatives, gelatine, animal and vegetable oils, polyethylene glycols, solvents and excipients conventionally used in the pharmaceutical art.

The compositions according to the invention may, if desired, additionally comprise further pharmacologically active ingredients such as, for example, diuretics, saluretics, α- and especially β-sympatholytics, tranquillisers, blood-vessel-dilating agents and anti-hypertensives.

Pharmacological Tests.

The effect on blood-pressure of compounds of general formula I according to the invention has been investigated in animal experiments using normotonic bastard dogs of both sexes under sodium pentobarbital anaesthesia (35—40 mg/kg i.p.).

During the tests the animals were laid on an operating table heated to 37°C and breathed spontaneously through a tracheal tube. To prevent blood coagulation they received a 2 mg/kg of heparin i.v.

The compounds tested were administered

(a) intravenously (i.v.) in aqueous solution through a polyvinyl chloride catheter into the femoral vein. The administration time was in each case 30 seconds; or

(b) intraduodenally (i.d.) in the form of carboxymethyl cellulose suspensions through a polyvinyl chloride catheter into the duodenum.

The following cardio-vascular parameters were measured:

1. p = average arterial blood pressure measured in mmHg through a polyvinyl chloride catheter using a Statham electronic pressure pick-up,

2. heart frequency (min^{-1}) measured by an ECG (electrocardiogram) (II, extremity derivation) by counting the R peaks, and

3. dp/dt_{max} (mmHg. sec^{-1}) by means of a differentiator.

The most important test results are summarised in Table 1.

For comparison, the commercially available anti-hypertensive, prazosin, (1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-(2-furoyl)-piperazine hydrochloride) was used. With this compound blood-pressure reduction is generally accompanied by an undesirable tachycardia. In contrast, the compounds according to the invention which we have tested generally show a bradycardiac action and therefore relieve the heart. The pressor reaction to catecholamines delivered exogenically is only inhibited moderately by the compounds while the comparison compound provokes a complete blockage of the α-receptors which give rise to a reversal of the adrenalin reaction.

Thus, the compounds of formula I tested have shown no α-sympathiocolytic activity on the isolated seminal vesicle of the guinea pig, whereas prazosin has a strong α-sympathicolytic activity comparable to phentolamine.

In the following Table I, n indicates the number of animals tested.

TABLE 1: Blood-pressure-reducing activity.

Compound of Example	Dose in mg/kg	Route of application	n	Maximum reduction of average arterial blood pressure in %	Interval till starting value of blood pressure is regained in min
2	30	i. d.	2	– 27	63
	50		2	– 32	52
10	3	i. v.	3	– 11	8
	6		3	– 16	14
	20	i. d.	4	– 19	37
	30		2	– 24	>100
	50		6	– 37	>55
12	20	i. d.	2	– 18	66
	50		2	– 43	118
13	3	i. v.	2	– 14	9
	6		2	– 19	16
	20	i. d.	2	– 18	70
	50		2	– 33	>45
15	3	i. v.	2	– 28	7
	6		2	– 33	20
	20	i. d.	2	– 25	36
	50		2	– 34	68
19	3	i. v.	2	– 15	5
	6		2	– 20	16
	10	i. d.	1	– 31	>110
	20		1	– 37	>120
	30		1	– 50	85
	50		2	– 48	>100

TABLE 1: Blood-pressure-reducing activity (Continued).

Compound of Example	Dose in mg/kg	Route of application	n	Maximum reduction of average arterial blood pressure in %	Interval till starting value of blood pressure is regained in min
39	6	i. v.	2	– 30	33
50	6	i. v.	2	– 52	40
53	3	i. v.	2	– 40	170
	6		2	– 45	>45
	20	i. d.	2	– 38	170
	50		2	– 41	178
54	3	i. v.	3	– 42	>75
	6		2	– 42	>70
56	6	i. v.	2	– 48	>115
	20	i. d.	2	– 45	>220
58	3	i. v.	1	– 47	65
	6		1	– 52	150
	20	i. d.	2	– 40	>200

The following Examples serve to illustrate the preparation of compounds of general formula I. The structure of the compounds described below has been proved by elemental analysis and by reference to i.r. and ^{1}H-n.m.r. spectra.

Example 1.

a) Ethyl-*O*-(2,3-dihydroxypropyl)-acetohydroximate
(see Formula VIII, Table 3) (According to process a).

A solution of 23 g (1 gram atom) of metallic sodium in 500 ml of anhydrous ethanol at room temperature has added to it 103.1 g (1 mol) of ethyl acetohydroximate, the mixture is stirred for 30 minutes and then 188.8 g (1.7 mol) of 3-chloropropane-1,2-diol are added dropwise, the temperature rises to approximately 45°C. After heating for 3 hours with reflux the mixture is allowed to cool, filtered from the precipitated sodium chloride and the filtrate evaporated under reduced pressure. Fractional distillation under reduced pressure of the oily residue yields 114 g (64.5% of theory) of the title compound, boiling point (0.1 mm Hg) 34°C.
$C_7H_{13}NO_4$ (M.W. = 177.2).

b) *O*-(2,3-Dihydroxypropyl)-hydroxylamine hydrochloride
(see Table 2).

88.6 g (0.5 mol) of the ester produced by step a) above are mixed with 500 ml of 2N hydrochloric acid in order to remove the protecting group in the form of ethyl acetate, and heated for 15 minutes with reflux. After cooling, the solution is evaporated under reduced pressure and the solid residue is recrystallised from isopropanol, 67.1 g (93.4% of theory) of the title compound having a melting point of 87—88°C are obtained.

$C_3H_{10}ClNO_3$ (M.W. = 143.6).

Analysis: Calculated C 25.10% H 7.02% Cl 24.69% N 9.76%
Found C 25.38% H 7.20% Cl 24.78% N 9.55%

Example 2.

a) Ethyl-*O*-(3-phenoxy-2-hydroxypropyl)-acetohydroximate
(see formula IX, Table 3 (According to process a).

51.5 g (0.5 mol) of ethyl acetohydroximate are dissolved in 250 ml of dimethylformamide, 7 ml of triethylamine are added and mixed by stirring with 82.5 g (0.55 mol) of 1-phenoxy-2,3-epoxypropane. The reaction mixture is subsequently stirred for 48 hours at 50°C, a further 7.5 g (0.05 mol) of the epoxide being added after 24 hours. After distillation of the solvent under reduced pressure, fractional distillation of the oily residue under reduced pressure yields 108.5 g (85.7% of theory) of the title compound, boiling point (0.07 mm Hg) 127—129°C, melting point 41—43°C; $\alpha_D^{20} = 1.5109$, $C_{12}H_{19}NO_4$ (M.W. = 253.3).

Analysis: Calculated C 61.64% H 7.56% N 5.53%
Found C 61.86% H 7.60% N 5.44%

b) *O*-(3-Phenoxy-2-hydroxypropyl)-hydroxylamine hydrochloride
(see Table 2).

81.3 g (0.32 mol) of the ester prepared in step a) are dispersed in 320 ml of 2N hydrochloric acid and heated for 15 minutes with vigorous stirring and reflux, a clear solution is obtained which is evaporated to dryness after cooling under reduced pressure. Re-crystallisation of the crystalline crude product (70 g = 100% of theory) from ethanol with the addition of diethyl ether at boiling temperature until precipitation yields 66.8 g (95% of theory) of the title compound, which decomposes above 138°C with the evolution of gas.

$C_9H_{14}ClNO_3$ (M.W. = 219.7).

Analysis: Calculated C 49.21% H 6.42% Cl 16.14% N 6.38%
Found C 49.09% H 6.24% Cl 16.20% N 6.46%

Example 3.

O-[3-(3,4-Dichlorophenoxy)-2-hydroxypropyl]hydroxylamine hydrochloride
(see Table 2) (According to process b).

A solution of 16.3 g (0.1 mol) of 3,4-dichlorophenol and 10.1 g (0.1 mol) of triethylamine in 100 ml of dimethylformamide is mixed with 15.9 g (0.1 mol) of ethyl *O*-(2,3-epoxypropyl)-acetohydroximate and the reaction mixture is stirred for 40 hours at 95—100°C. Afterwards, the solvent is distilled off under reduced pressure and the residue fractionally distilled under reduced pressure to give 26.2 g (81.3% of theory) of ethyl *O*-[3-(3,4-dichlorophenoxy)-2-hydroxypropyl]-acetohydroximate of boiling point 3 mm Hg) 178—180°C. To give the hydroxylamine, the distillate (81.3 mmol) is heated in 100 ml of 2N hydrochloric acid for 15 minutes with reflux, the cooled solution is evaporated to dryness under reduced pressure and the soild residue is recrystallised from ethanol.

Yield: 16.4 g (70% of theory); melting point: 152°C (with decomposition).
$C_9H_{12}Cl_3NO_3$ (M.W. = 288.6).

Analysis: Calculated C 37.46% H 4.19% Cl 36.86% N 4.85%
Found C 37.43% H 4.29% Cl 36.42% N 4.83%

Example 4.

O-(3-Amino-2-hydroxypropyl)-hydroxylamine dihydrochloride
(see Table 2) (According to process b)

15.9 g (0.1 mol) of ethyl *O*-(2,3-epoxypropyl)-acetohydroximate are dissolved

in 165 ml of ethanol, mixed with 166 ml of an aqueous ammonia solution enriched with NH_3 gas (prepared by introducing NH_3 gas into 140 ml of 25% ammonia solution with ice cooling to a total volume of 166 ml) and shaken in a sealed pressure vessel for 17 hours at room temperature. Before the apparatus is opened the mixture is cooled to −30°C, the ammonia is allowed to partially escape at room temperature and the residue is evaporated together with a solvent under reduced pressure. The oily residue is mixed with 150 ml of 2N hydrochloric acid to remove the protecting group and stirred for 15 minutes at boiling temperature. It is then allowed to cool, the excess acid is removed under reduced pressure and the solid residue is re-crystallised from ethanol with the addition of diethyl ether at boiling heat until turbidity.

Yield: 9.2 g (51.4% of theory); melting point 155—156°C (with decomposition).

$C_5H_{12}Cl_2N_2O_2$ (M.W. = 179.1).

Analysis: Calculated C 20.13% H 6.76% Cl 39.60% N 15.65%
Found C 20.23% H 6.87% Cl 39.61% N 15.66%

The free base of this compound can be distilled off under reduced pressure without decomposition: boiling point (0.04 mm Hg) 100—103°C.

Example 5.

O-[3-(4-morpholinyl)-2-hydroxypropyl]-hydroxylamine dihydrochloride (see Table 2) (According to alternative process b).

A solution of 79.6 g (0.5 mol) of ethyl *O*-(2,3-epoxypropyl)acetohydroximate and 43.6 g (0.5 mol) of morpholine is heated in 300 ml of n-propanol for 4 hours with reflux. It is then allowed to cool, the alcohol is distilled off under reduced pressure, the residue mixed with 750 ml of 2N hydrochloric acid and the mixture boiled for 15 minutes with vigorous stirring. The mixture is then evaporated under reduced pressure and the solid crude product is re-crystallised from methanol with the addition of diethyl ether at boiling heat until precipitation.

Yield: 112.7 g (90.5% of theory); melting point 178—180°C (with decomposition).

$C_7H_{18}Cl_2N_2O_3$ (M.W. = 249.1).

Analysis: Calculated C 33.75% H 7.28% Cl 28.46% N 11.24%
Found C 33.54% H 7.46% Cl 28.34% N 11.04%

The same compound may be obtained by analogous reaction of equimolar quantities of morpholine and methyl *O*-(2,3-epoxypropyl)-benzohydroximate with a yield of 98% of theory.

The free basis of the dihydrochloride can be isolated in crystalline form. After re-crystallisation from diisopropyl ether it has a melting point of 80—81°C; $C_7H_{16}N_2O_3$ (M.W. = 176.2).

Analysis: Calculated C 47.71% H 9.15% N 15.90%
Found C 47.96% H 9.35% N 15.99%

Example 6.

O-[3-(1-Imidazolyl)-2-hydroxypropyl]-hydroxylamine dihydrochloride (see Table 2 (According to process b).

A solution of 127.4 g (0.8 mol) of ethyl *O*-(2,3-epoxypropyl)-acetohydroximate and 54.5 g (0.8 mol) of imidazole in 500 ml of dimethylformamide is mixed with 15 ml of triethylamine and the mixture is stirred for 35 hours at 80°C. The oil obtained after evaporation under reduced pressure is dissolved in 500 ml of 4N hydrochloric acid and heated for 15 minutes with reflux. The mixture is subsequently evaporated to dryness under reduced pressure and the residue is re-crystallised from ethanol.

Yield: 129 g (70.1% of theory); melting point 132°C; $C_6H_{13}Cl_2N_3O_2$ (M.W. = 230.1).

Analysis: Calculated C 31.32% H 5.70% Cl 30.82% N 18.26%
Found C 31.01% H 5.92% Cl 30.56% N 18.04%

Example 7.
1,3-bis-Amino-oxy-2-hydroxypropane dihydrochloride
(see Table 2).

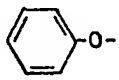
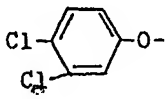
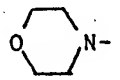
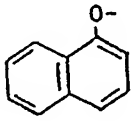
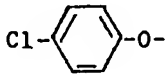
10.3 g (0.1 mol) of ethyl acetohydroximate is added to a solution of 2.3 g (0.1 gram atom) of sodium in 100 ml of anhydrous methanol at room temperature, the mixture is stirred for 30 minutes and the alcohol distilled off under reduced pressure. The sodium salt thus obtained is suspended in 100 ml of dry dioxan and mixed dropwise with 15.9 g (0.1 mole) of ethyl *O*-(2,3-epoxypropyl)acetohydroximate with vigorous stirring. The mixture is then treated for 3 hours with reflux, the solvent is removed under reduced pressure, and the residue dissolved in water. The alkaline solution obtained is neutralised with 2N hydrochloric acid and the 1,3-bis-(1-ethoxy-ethylidene-amino-oxy)-2-hydroxypropane of formula (VII) ($R^4 = CH_3$ and $R^5 = C_2H_5$) is extracted with ethyl acetate. Evaporation of the organic phase under reduced pressure after drying over sodium sulphate, yields an oily residue which after dissolving in 100 ml of 2N hydrochloric acid is boiled for 15 minutes with reflux. Removal of the solvent under reduced pressure and re-crystallisation of the solid residue from ethanol with the addition of diethyl ether at boiling temperature until turbidity yields 10 g (52% of theory) of the title compound having a melting point of 155—156°C. $C_3H_{12}Cl_2N_2O_3$ (M.W. = 195.1).

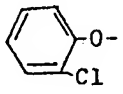
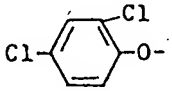
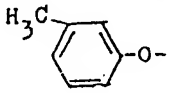
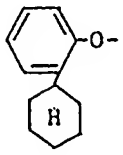
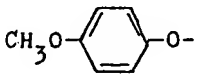
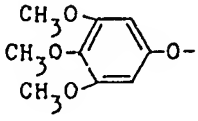
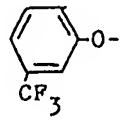
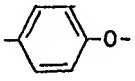
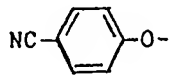
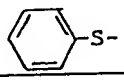
Analysis: Calculated C 18.47% H 6.20% Cl 36.35% N 14.36%
Found C 18.86% H 6.48% Cl 36.37% N 14.07%

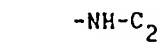
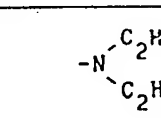
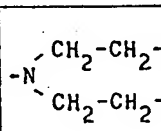
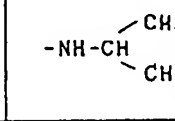
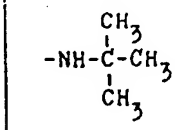
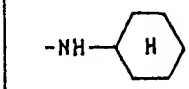
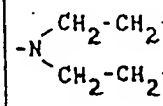
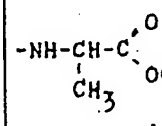
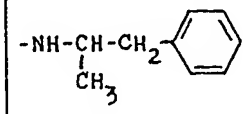
The compounds listed in the following Table 2 may be prepared analogously according to processes a) and/or b):

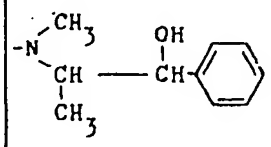
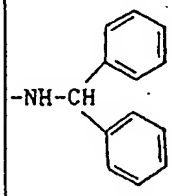
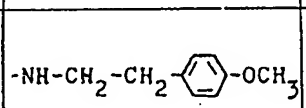
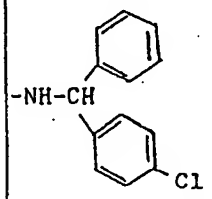
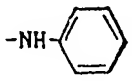
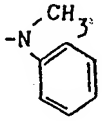
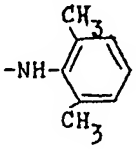
Table 2: Examples according to formula

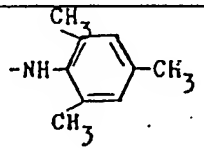
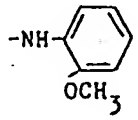
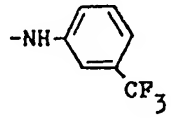
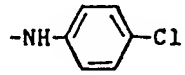
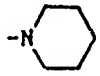
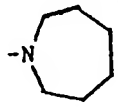
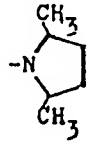
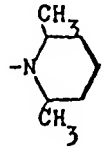
$$H_2N\text{-}O\text{-}CH_2\text{-}\underset{\underset{OH}{|}}{CH}\text{-}CH_2\text{-}X \quad (I)$$

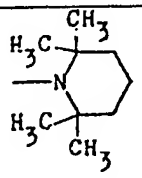
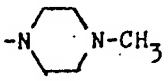
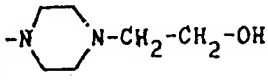
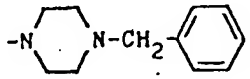
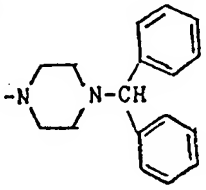
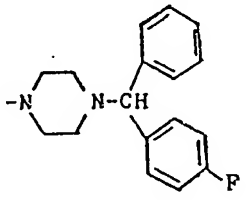
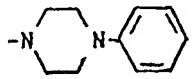
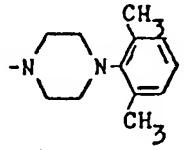
Example	X	Process	isolated as	Melting or boiling point (mm Hg)°C
1	OH -	a	1 HCl	87- 88
2		a	1 HCl	138 (decomp.)
3		b	1 HCl	152 (decomp.)
4	H_2N-	b	2 HCl	155-156(decomp)
5		b	2 HCl Base	178-180(decomp) 80- 81
6		b	2 HCl	132
7	H_2N-O-	a/b	2 HCl	155-156
8	CH_3-$(CH_2)_3$-O-	a	Base	97-101 (0,2)
9		a	Base 1 HCl	65-67(decomp.) 193-194(decomp)
10		a	1 HCl	170-172

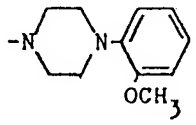
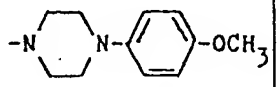
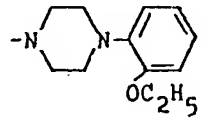
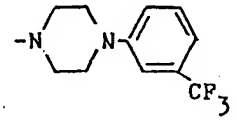
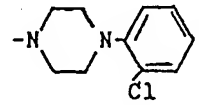
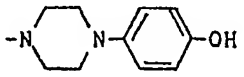
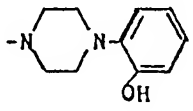
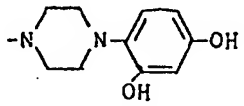
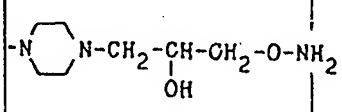
Example	X	Process	isolated as	Melting or boiling point (mm Hg) °C
11		a	1 HCl	154-155
12		a	1 HCl	160
13		a	1 HCl	165-167
14		a	1 HCl	119-120
15		a	1 HCl	140-142
16		b	1 HCl	176
17		b	1 HCl	159-160 (decomp.)
18		a	1 HCl	178-179
19		a	1 HCl	167
20		a and	1 HCl	120-121

Example	X	Process	isolated as	Melting or boiling point (mm Hg)°C
21		b	Base	Oil
22		b	Base	80 (0,3)
23		b	2 HCl	Oil
24		b	2 HCl	155-157 (decomp.)
25		b	Base 2 HCl	102 (0,5) 188
26		b	Base	Oil
27		b	Base	145 (0,5)
28		b	2 HCl	strongly hygroscopic
29		b	2 HCl	141-142 (decomp.)

Example	X	Process	isolated as	Melting or boiling point (mm Hg)°C
30		b	2 HCl x 1 C_2H_5OH	strongly hygroscopic
31		b	2 HCl	179-180 (decomp.)
32		b	2 HCl	157-158 (decomp.)
33		b	2 HCl	185-186 (decomp.)
34		b	2 HCl	168-170 (decomp.)
35		b	Base	150 (0,3) Fp. 50° C
36		b	2 HCl	213-214 (decomp.)

Example	X	Process	isolated as	Melting or boiling point (mm Hg) °C
37		b	2 HCl	200 (decomp.)
38		b	2 HCl	175-176 (decomp.)
39		b	2 HCl	175-176 (decomp.)
40		b	2 HCl	179-181 (decomp.)
41		b	2 HCl	154 (decomp.)
42		b	2 HCl	oil
43		b	Base 1 HCl	110-112 (0,2) 92
44		b	Base 1 HCl	101 (0,03) 110-112
45		b	Base 1 HCl	120 (0,2) 138-140

Example	X	Process	isolated as	Melting or boiling point (mm Hg) °C
46		b	2 HCl	Oil
47		b	3 HCl	187 (decomp.)
48		b	3 HCl x¹ 1 H_2O	115
49		b	3 HCl	184-185 (decomp.)
50		b	fumarate 3 HCl	182-183 from 168 (decomp.)
51		b	3 HCl	166-168 (decomp.)
52		b	3 HCl	178-179 (decomp.)
53			2 HCl	152-154

Example	X	Process	isolated as	Melting or boiling point (mm Hg) °C
54		b	3 HCl x 1 H_2O	142 (decomp.)
55		b	3 HCl	153-155 (decomp.)
56		b	1 HCl	153-154 (decomp.)
57		b	2 HCl	197-198
58		b	2 HCl	177-178 (decomp.)
59		b	3 HCl	192-194 (decomp.)
60		b	3 HCl	182-184 (decomp)
61		b	2 HCl	178-179 (decomp.)
62		b	4 HCl	188-190 (decomp.)

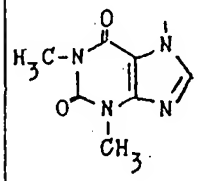
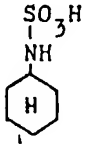
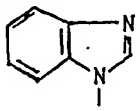
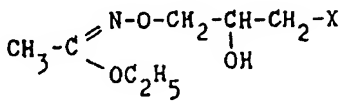
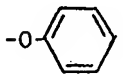
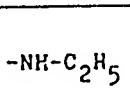
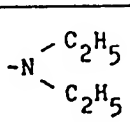
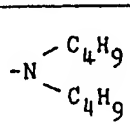
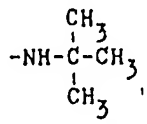
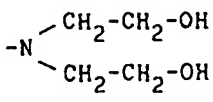
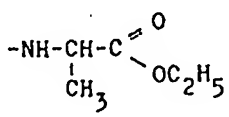
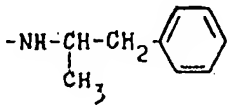
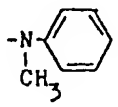
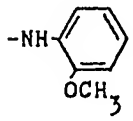
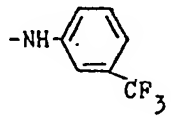
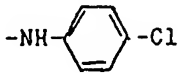
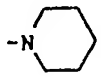
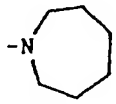
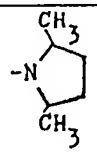
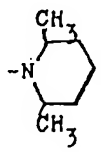
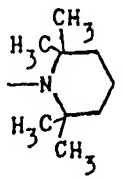
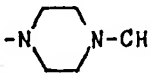
Example	X	Process	isolated as	Melting or boiling point (mm Hg)°C
63		b	2 HCl	108-109
64		b		153-154
65		b	1 HCl Cyclamate	138-140(decomp) 122-123
66	-NHOH	b	2 HCl	from 54 (decomp.)

Table 3:
Further intermediate compounds of formula



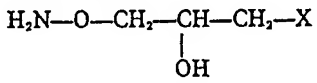
X	Melting or boiling point (mm Hg) in °C
-OH (VIII)	34 (0.1)
 (IX)	127-129 (0.07) 41- 43
	66
	98 (0.5)
	142-145 (0.5)
	105-108 °(0.2)
	175-180 (0.5)
	148-150 (0 05)

X	Melting or boiling point (mm Hg) in °C
	167-170 (0.05)
	148 (0.3)
	173-176 (0.08)
	138-141 (0.01)
	175-178 (0.05)
	105 (0.5)
	130-132 (0.5)
	111-115 (0.5)
	138 (0.3)

X	Melting or boiling point (mm Hg) in °C
	134-136 (0.5)
	165 (0.2)

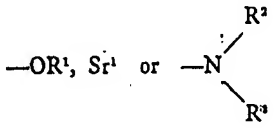
WHAT WE CLAIM IS:—

1. Compounds of general formula



(I)

[wherein X represents a group of the formula



(in which R^1 represents

a) a hydrogen atom,
b) an amino group, when X represents an $—OR^1$ moiety,
c) an alkyl group having from 1 to 6 carbon atoms or
d) a mono- or binuclear aryl group optionally substituted by one or more halogen atoms or alkyl, alkoxy, halogenoalkyl groups each having up to 4 carbon atoms, cycloalkyl groups having 3 to 6 carbon atoms, nitro or cyano groups; and

R^2 and R^3, which may be the same or different, each represents

a) a hydrogen atom,
b) an alkyl group having from 1 to 6 carbon atoms or cycloalkyl groups having from 3 to 7 carbon atoms and optionally substituted by one or more hydroxy groups or alkoxycarbonyl groups having 1 to 4 carbon atoms,
c) an aralkyl or diaralkyl group having 1 to 4 carbon atoms in the alkyl moiety and being optionally substituted in the alkyl moiety by hydroxy groups, and optionally substituted in the aryl moieties by one or more alkoxy groups having from 1 to 4 carbon atoms or halogen atoms,
d) a mono- or binuclear aryl group optionally substituted by one or more alkyl, alkoxy or halogenoalkyl groups each having up to 4 carbon atoms or halogen atoms,
e) a hydroxy group when the other of R^2 and R^3 is hydrogen, or
f) R^2 and R^3, together with the nitrogen atom to which they are attached, represent a 5- to 7-membered saturated ring optionally substituted by an alkyl or hydroxyalkyl group each having from 1 to 4 carbon atoms, an aralkyl or diaralkyl group each having up to 4 carbon atoms in the alkyl moiety and the aryl moieties thereof are optionally substituted by one or more halogen atoms, a mono- or binuclear aryl group optionally substituted by at least one alkyl, alkoxy or halogenoalkyl group each having up to 4 carbon atoms, or by one or more halogen atoms or hydroxy groups, or by

a 3-aminooxy-2-hydroxypropyl group, and the ring being optionally interrupted by an oxygen, sulphur or further nitrogen atom or sulphonyl group, or

g) R^2 and R^3 together with the nitrogen atom to which they are attached, represent a 5-membered heteroaromatic ring containing up to 4 nitrogen atoms and being optionally fused to one or more benzene or optionally substituted uracil rings)]

and physiologically acceptable acid addition salts thereof.

2. Compounds as claimed in claim 1 wherein R^2 and R^3 together with the nitrogen atom to which they are attached form a 5- to 7-membered ring having a further nitrogen hetero-atom which is substituted by an alkyl or hydroxyalkyl group each having up to 4 carbon atoms; an aralkyl or diarylalkyl group each having up to 4 carbon atoms in the alkyl moiety and the aryl radicals thereof are optionally substituted by one or more halogen atoms; a mono- or binuclear aryl group optionally substituted by at least one alkyl, alkoxy, or halogenoalkyl group each having up to 4 carbon atoms, or by one or more halogen atoms or hydroxy groups; or by a 3-aminooxy-2-hydroxypropyl group.

3. Compounds as claimed in either of claims 1 and 2 wherein aryl groups in any of R^1, R^2 and R^3 are substituted up to 3 times.

4. Compounds as claimed in any of the preceding claims wherein halogenoalkyl radicals in R^1, R^2 and R^3 contain at most two carbon atoms.

5. Compounds as claimed in any of the preceding claims wherein R^1 and R^2 is an optionally substituted phenyl group.

6. Compounds as claimed in any of the preceding claims in the form of optically active isomers.

7. *O*-(3-Phenoxy-2-hydroxypropyl)-hydroxylamine and physiologically acceptable acid addition salts thereof.

8. *O*-[3-(*p*-Chlorophenoxy)-2-hydroxypropyl]-hydroxylamine and physiologically acceptable acid addition salts thereof.

9. *O*-[3-(2,4-Dichlorophenoxy)-2-hydroxypropyl]-hydroxylamine and physiologically acceptable acid addition salts thereof.

10. *O*-[3-(3-Methylphenoxy)-2-hydroxypropyl]-hydroxylamine and physiologically acceptable acid addition salts thereof.

11. *O*-[3-(4-Methoxyphenoxy)-2-hydroxypropyl]-hydroxylamine and physiologically acceptable acid addition salts thereof.

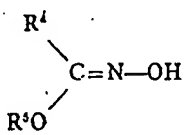
12. *O*-[3-(4-Cyanophenoxy)-2-hydroxypropyl]-hydroxylamine and physiologically acceptable acid addition salts thereof.

13. *O*-[3-(3-Trifluoromethyl-anilino)-2-hydroxypropyl]-hydroxylamine and physiologically acceptable acid addition salts thereof.

14. *O*-[3-(4-Diphenylmethyl-piperazin-1-yl)-2-hydroxypropyl]-hydroxylamine and physiologically acceptable acid addition salts thereof.

15. Compounds of general formula I as defined in claim 1 as herein specifically disclosed, with the exception of those compounds claimed in claims 7 to 14.

16. A process for the preparation of compounds of general formula I as claimed in claim 1 which comprises reacting a hydroximic acid ester of formula

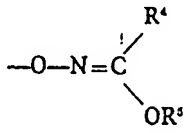


(II)

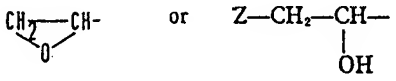
(in which R^4 represents a straight-chained or branched alkyl group having from 1 to 6 carbon atoms or a mono- or binuclear aryl group optionally substituted by one or more alkyl or alkoxy groups each having up to 2 carbon atoms or halogen atoms; and R^5 represents a straight-chained or branched alkyl group having from 1 to 6 carbon atoms) or a salt thereof with a compound of formula

$$Y—CH_2—R^6 \qquad \text{(III)}$$

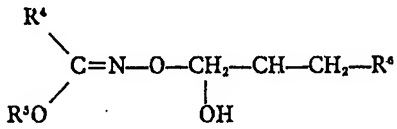
[in which R^6 is as defined in claim 1 for X or represents a group of the formula



(in which R^4 and R^5 are as hereinbefore defined) and Y represents a group of the formula

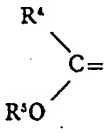


(in which Z represents a halogen atom or a reactive sulphonic acid ester group to form a compound of the formula



(VI)

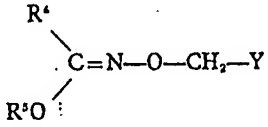
(in which R^4, R^5 and R^6 are as hereinbefore defined) and subsequently removing the protecting group of formula



(in which R^4 and R^5 are as hereinbefore defined).

17. A process as claimed in claim 16 wherein the reaction of the compound of formula II with the compound of formula III is effected in a solvent comprising an alcohol and thecompound of formula III is in the form of an alkali metal or alkaline-earth metal salt.

18. A process for the preparation of compounds of general formula I as defined in claim 1 which comprises reacting an *O*-alkylated hydroxylamine derivative of formula

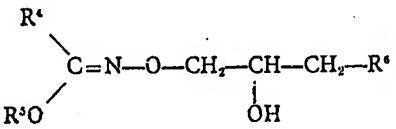


(IV)

(in which R^4, R^5 and Y are as defined in claim 16) with a compound of formula

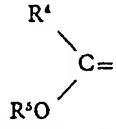
$$H—R^6 \qquad (V)$$

(in which R^6 is as defined in claim 16) to form a compound of formula



(VI)

(in which R^4, R^5 and R^6 are as defined in claim 16) and subsequently removing the protecting group of formula



(in which R^4 and R^5 are as defined in claim 16).

19. A process as claimed in claim 18 wherein the compound of formula IV is an alkyl *O*-(2,3-epoxypropyl)-benzohydroximate or alkyl *O*-(2,3-epoxypropyl)-acetohydroximate.

20. A process as claimed in claim 19 wherein the alkyl group contains up to 4 carbon atoms.

21. A process as claimed in claim 20 wherein the alkyl group is a methyl or ethyl group..

22. A process as claimed in any of claims 16 to 21 wherein Z represents a chlorine or bromine atom.

23. A process as claimed in any of claims 16 to 22 wherein the first reaction is effected at a temperature of from 0 to 200°C.

24. A process as claimed in claim 23 wherein the reaction is effected at a temperature of from 50°C to the boiling point of the reaction mixture.

25. A process as claimed in any of claims 16 to 24 wherein the first reaction is performed in the presence of a base.

26. A process as claimed in claim 25 wherein the base comprises an alkali metal or alkaline earth metal hydroxide, carbonate, hydride or alcoholate, or triethylamine, pyridine, picoline or quinoline.

27. A process as claimed in any of claims 16 to 26 wherein the first reaction is effected in the presence of a solvent which is inert under the reaction conditions.

28. A process as claimed in claim 27 wherein the reaction is effected in the presence of dimethylformamide and a catalyst comprising trimethylamine.

29. A process as claimed in claim 28 wherein the reaction is effected at a temperature of from 50 to 100°C.

30. A process as claimed in any of claims 16 to 29 wherein the protecting group is removed hydrolytically.

31. A process as claimed in claim 30 wherein the hydrolytic removal of the protecting group is effected without isolation of the intermediate compound of formula IV.

32. A process as claimed in either of claims 30 and 31 wherein the hydrolytic removal of the protecting group is effected in an aqueous, aqueous alcoholic or aqueous etheric medium.

33. A process as claimed in claim 32 wherein the removal of the protecting group is effected at a temperature of from 0 to 120°C.

34. A process as claimed in claim 33 wherein the removal of the protecting group is effected at a temperature of from 60 to 110°C.

35. A process as claimed in any of claims 16 to 34 wherein a free base of the compound of formula I produced is converted to a physiologically acceptable acid addition salt thereof.

36. A process as claimed in any of claims 16 to 35 wherein a racemate of the compound of formula I or a physiologically acceptable acid addition salt thereof is resolved into its individual optical isomers.

37. A process as claimed in any of claims 16 to 35 wherein the process is carried out using an enantiomeric material and an optically active compound of formula I or a physiologically acceptable acid addition salt thereof is obtained.

38. A process as claimed in any of claims 16 to 37 substantially as herein described.

39. A process as claimed in any of claims 16 to 38 substantially as described herein with reference to the Examples.

40. A pharmaceutical composition comprising as active ingredient at least one compound of formula I as defined in claim 1 or a physiologically acceptable acid addition salt thereof in association with a pharmaceutical carrier or excipient.

41. A composition as claimed in claim 40 in a form suitable for oral or parenteral administration.

42. A composition as claimed in claim 41 in the form of powders, tablets, syrups, capsules, emulsions, suspensions, drops, injectable solutions or forms adapted to provide a sustained release of active ingredient.

43. A composition as claimed in any of claims 40 to 42 comprising at least one further pharmacologically active ingredient.

44. A composition as claimed in claim 43 wherein the further active ingredient comprises a diuretic, saluretic, α- or β-sympatholytic, tranquilliser, a blood-vessel dilating substance or an antihypertensive.

45. A pharmaceutical composition as claimed in claim 40 substantially as herein described.

46. Compounds of general formula I as defined in claim 1 or a physiologically acceptable acid addition salt thereof whenever prepared by a process claimed in any of claims 16 to 39.

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